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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/654,994	09/05/2003	Mark W.J. Ferguson	39-288	6683

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/654,994	FERGUSON, MARK W.J.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-27* is/are pending in the application.

4a) Of the above claim(s) *23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-22 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *20-27* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0903*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 20–27 are pending.

Applicant's election with traverse of the species activin in the reply filed on 07/17/2006 is acknowledged. The traversal is on the ground(s) that a thorough search of the relevant art would necessarily encompass all of the enumerated species, and that accordingly no undue burden would be placed on the Examiner from a searching perspective if the requirement for election were to be withdrawn. This is not found persuasive because the claims are directed to encompass activin, modified forms of activin, indeterminate inhibitors of activin metabolism, indeterminate stimulators of activin synthesis, and indeterminate activin agonists. Clearly the species are not sufficiently few in number such that a search and examination of the entire claimed invention can be made without serious burden. The indeterminate compounds and activin are clearly are not so closely related that a search and examination of the entire claimed invention can be made without serious burden. The indeterminate compounds and activin clearly do not share a substantial structural feature essential to a shared common utility. The indeterminate compounds and activin are so unrelated and diverse that a prior art reference anticipating the claim with respect to one would not render the claim obvious under 35 U.S.C. 103 with respect to the other. In such a case the examiner may require a provisional election of a single species prior to examination on the merits. In addition, unity of invention does not exist if the inventive concept does not make a contribution over the prior art. With respect to the present claims, the inventive concept does not make a contribution over the prior art because of the prior art rejections, below. Therefore, the Markush group does not fulfill the requirements for unity of invention

The requirement is still deemed proper and is therefore made FINAL.

Claims 20–27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), to the extent that they are drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 07/17/2006.

Claims 20–22 and 24–27 are being examined to the extent that they are directed to or encompass the elected species activin.

The following passages from the specification seem most relevant for construing the breadth of the claims and the applicability of the prior art:

> By "wounds or fibrotic disorders" is meant any condition which may result, in the formation of scar tissue. In particular, this includes the healing of skin wounds, the repair of tendon damage, the healing of crush injuries, the healing of eye wounds, including wounds to the cornea, the healing of central nervous system (CNS) injuries, conditions which result in the formation of scar tissue in the CNS, scar tissue formation resulting from strokes, and tissue adhesion, for example, as a result of injury or surgery (this may apply to e.g. tendon healing and abdominal strictures and adhesions). Examples of fibrotic disorders include pulmonary fibrosis, glomerulonephritis, cirrhosis of the liver, systemic sclerosis, scleroderma, proliferative vitreoretinopathy, repair following myocardial infarction, including myocardial hibernation. Page 1, full paragraph 2.
>
> There is also a lack of compositions for use in the treatment of chronic wounds, for example venous ulcers, diabetic ulcers and bed sores (decubitus ulcers), especially in the elderly and wheel chair bound patients. Such compositions may be extremely useful in patients where wound healing is either slow or in whom the wound healing process has not yet started. Such compositions may be used to "kick-start" wound healing and may then be used in combination with compositions (e.g. those of PCT/GB93/00586) which promote the healing of wounds or fibrotic disorders with reduced scarring. Hence not only may a chronic wound be healed, but it may be healed with, reduced scarring. Page 2, full paragraph 1.
>
> By `stimulator` is meant anything which may stimulate the quantity or efficacy of active Activin and/or active Inhibin at a site. This may be Activin or Inhibin itself (or a pharmaceutically acceptable salt thereof) or a fragment or a partially modified form thereof. Partial modification may for example be by way of addition, deletion or substitution of amino acid residues. A substitution may for example be a conserved

substitution. Partially modified molecules may, for example, have a longer half-life than their parent molecule, or they may have a different binding affinity for their receptors. A fragment may comprise a least that part of Activin or Inhibin which is required to allow it to stimulate its receptors. Alternatively, a stimulator may, for example, be an inhibitor of Activin metabolism, or it may be a stimulator of Activin synthesis, or it may be a bioprecursor of activin or inhibin. For example, it may be an analogue of a fragment of activin or inhibin which is bound by a degradative enzyme, for example a mimotope. (Geysen, H. M. et al., 1987, Journal of Immunological Methods, 102, 259-274) made to a fragment of Activin or Inhibin which is bound by enzyme which degrades it. Such a mimotope can bind to the receptor site of the enzyme, competitively inhibiting the binding of Activin or Inhibin (as appropriate) to the enzyme and thereby inhibiting its degradation. Paragraph bridging pages 2-3.

It may be an antagonist of an antagonist of Activin or Inhibin. For example, it may be an antagonist of Follistatin. Page 3, full paragraph 1.

Activin is a member of the TGF-β superfamily, and like the other members of this family, activins are dimeric proteins, composed of disulphide linked beta A or beta B subunits. Three different forms of Activin have been identified in vivo: Activin A (beta a, beta a), Activin B (beta b, beta b) and Activin AB (beta a, beta b). Herein, by "Activin" is meant all possible forms of activin. Page 3, full paragraph 2.

There have been no reports of the role of either Activin, Inhibin or follistatin during wound healing, scarring or fibrosis.

However, the present inventor has found that Activin and Inhibin in fact play roles in wound healing as non-fibrotic growth factors. High levels of expression of Activin and of Activin and Inhibin receptors have been found post-wounding at wound sites, similar to TGF-β_3 (see PCT/GB93/00586). Ibis observation is particularly surprising in light of the prior belief that. Activin and Inhibin are predominantly reproductive/erythroid/neurological/mesoderm inducing factors.

Activin and Inhibin have been found to be structurally similar to TGF-β_3, the similarity being greater than that with TGF-β_1 and TGF-β_2. It appears that Activin and Inhibin may in fact bind to receptors similar to those bound by TGF-β_3 and as such mediate the control of scarring via that route.

It has also been found that the Act 2a receptor, which is bound by Activin and which is believed to be bound by TGF-β_3, is upregulated in wound healing, especially on day 7 post-wounding. Table 1 details further the binding of the isoforms of the TGF-β receptor family.

Hence Activin and Inhibin have similar anti-scarring properties to those of TGF-β_3 and as

such Activin and Inhibin, may be used to similar effect (see, for example, PCT/GB93/00586). Page 5.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20–22 and 24–27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to or encompass a "stimulator of activin." The specification intends such a "stimulator" to be anything which may stimulate the quantity or efficacy of active Activin (paragraph bridging pages 2-3). Accoridngly, the claims are directed to or encompass an indeterminate genus of activin stimulators.

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention. Thus, an applicant complies with the written description requirement by describing the invention, with all its claimed limitations, not that which makes it obvious, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.

An adequate written description of a "stimulator of activin" requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for

obtaining such. Accordingly, an adequate written description of a "stimulator of activin" requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the stimulator itself.

The specification and claims do not indicate what distinguishing attributes are shared by the members of the indeterminate genus of activin stimulators. Structural features that could distinguish compounds in the genus from other compounds are missing from the disclosure. No common structural attributes identify the members of the genus.

Whereas the instant specification provides a detailed description of reduced scarring and wound healing with activin, the instant specification does not provide a structural formula which is definitive of all activin stimulators. Whereas the instant specification may identify a functional property which is common to "a stimulator of activin," it does not identify those defining structural elements which provide the structural and functional properties of all such stimulators. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is indeterminate, one of skill in the art would reasonably conclude that the disclosure fails to describe the genus. Thus, applicant was not in possession of the genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20–22 and 24–25 are rejected under 35 U.S.C. 102(e) as being anticipated by Mitrani (U. S. Patent No. 5753612).

Mitrani discloses pharmaceutical preparations for controlling the proliferation of ectodermally-derived tissue, such as in the treatment of disorders marked by aberrant proliferation or in the repair of damaged tissue, which preparations comprise, as an active ingredient, an agent ("activin agonist") which mimics the inhibitory effect of activin or a related polypeptide factor, which activin agonist is provided in a pharmaceutically acceptable carrier or diluent. Mitrani's invention also relates to methods of controlling proliferation of ectodermally-derived tissue by use of the pharmaceutical preparations of the invention. See column 6, full paragraph 4. Mitrani's method that can be used to control wound healing processes, as for example may be desirable in connection with any surgery involving epithelial tissue, such as from dermatological or periodontal surgeries. Exemplary surgical repair for which activin therapy is a candidate treatment include severe burn and skin regeneration, skin grafts, pressure sores, diabetic ulcers, fissures, post surgery scar reduction, and ulcerative colitis. See paragraph bridging columns 6-7. The term "activin agonist" refers to molecules which inhibit proliferation of epithelial and other ectodermally-derived cells by mimicking the antiproliferative effects of activin A or a related activin factor. In particular, the term "activin agonist" encompasses polypeptides (such as preparations of activin-A itself) and peptidyl fragments thereof. See column 7, full paragraph 4.

Claims 20–22 and 24–25 are rejected under 35 U.S.C. 102(b) as being anticipated by De Krester (U. S. Patent No. 5196192).

The claims are directed to a method comprising administering to a subject in need of treatment a therapeutically effective amount of a stimulator of activin. The claims do not limit what treatment a subject is in need of. The recitation of "for promoting the healing of fibrotic disorders with reduced scarring" and "for promoting the healing with reduced scarring" occur in the claim preamble and have not been given patentable weight. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps are able to stand alone. Accordingly, the claims do not limit what treatment a subject is in need of.

De Krester provides a method for treating a wound including a surgical lesion, burn, tissue graft or chronic ulcer in a host in need of such treatment which method comprises administering to said host a growth promoting amount of a growth promoter comprising activin or an activin composition (column 5, full paragraph 5). De Krester further provides a method of using activin for the preparation of pharmaceutical composition for promotion of tissue regeneration in a wound including a surgical lesion, burn, tissue graft or chronic ulcer (column 7, full paragraph 1). See also column 7, line 54 through paragraph bridging columns 7-8; paragraph bridging columns 12-13 through column 13, full paragraph 3.

It almost goes without saying that a host with a surgical lesion, burn, tissue graft or chronic ulcer is "a subject in need of treatment." The specification intends a "stimulator of activin" to be anything which may stimulate the quantity or efficacy of active Activin, including

activin itself (paragraph bridging pages 2-3). Accordingly, De Krester discloses a method of promoting the healing of wounds comprising administering to a subject in need treatment a therapeutically effective amount of activin. Furthermore, even if one were to give the claim preambles patentable weight and although De Krester is silent as to reduced scaring, the examiner concludes that reduced scarring is an inherent property of De Krester's method. In addition, the specification intends "wounds or fibrotic disorders" to encompass any condition which may result, in the formation of scar tissue (page 1, full paragraph 2) and specifically mentions surgical wounds and chronic ulcers (page 1, full paragraph 2 and page 2, full paragraph 1), which are also mentioned by De Krester as candidates for activin treatment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20–21 and 26–27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitrani (U. S. Patent No. 5753612) as applied to claims 20–21 above, and further in view of Ferguson (WO 92/17206).

Mitrani discloses methods for treating fibrotic disorders and promoting healing with reduced scarring by administering activin, as discussed above. Mitrani does not teach, only in the sense that Mitrani does not anticipate, a method wherein the activin is used in conjunction with a further agent that promotes the reduction of scarring or wherein the activin is used in conjunction with a further agent that promotes eth healing of chronic wounds.

Ferguson discloses compositions comprising agents to accelerate wound healing and combinations of growth factor neutralizing agents that reduce wound scarring (page 7, full paragraph 3; paragraph bridging pages 11-12; paragraph bridging pages 12-13; page 13, full paragraph 1). Other growth factors are believed to act in cooperation with one another in the complex overall regulatory process that is involved in wound healing (paragraph bridging pages 4-5). The overall process of wound healing is regulated by a number of growth factors (paragraph bridging pages 2-3). Ferguson does not teach a method for treating fibrotic disorders and promoting healing with reduced scarring by administering activin.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to treat fibrotic disorders and promote healing with reduced scarring by administering activin, as taught by Mitrani, and to modify that teaching by using the activin in conjunction with a further agent that promotes the reduction of scarring or further agent that promotes the healing of chronic wounds, as taught by Ferguson, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because the overall process of wound healing is regulated by a number of growth factors and the combined administration of two or more scar reducing agents may be found to be even more effective or the combined administration of anti-scarring agent and a healing promoting agent would be expected to result in faster wound healing. The invention is prima facie obvious over the prior art.

Claims 20–21 and 26–27 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Krester (U. S. Patent No. 5196192) as applied to claims 20–21 above, and further in view of Ferguson (WO 92/17206).

De Krester discloses a method of promoting the healing of wounds comprising administering to a subject in need treatment a therapeutically effective amount of activin. De Krester does not teach, only in the sense that De Krester does not anticipate, a method wherein the activin is used in conjunction with a further agent that promotes the reduction of scarring or wherein the activin is used in conjunction with a further agent that promotes eth healing of chronic wounds.

Ferguson discloses compositions comprising agents to accelerate wound healing and combinations of growth factor neutralizing agents that reduce wound scarring (page 7, full paragraph 3; paragraph bridging pages 11-12; paragraph bridging pages 12-13; page 13, full paragraph 1). Other growth factors are believed to act in cooperation with one another in the complex overall regulatory process that is involved in wound healing (paragraph bridging pages 4-5). The overall process of wound healing is regulated by a number of growth factors (paragraph bridging pages 2-3). Ferguson does not teach a method for treating fibrotic disorders and promoting healing with reduced scarring by administering activin.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to promote the healing of wounds comprising administering to a subject in need treatment a therapeutically effective amount of activin, as taught by De Krester, and to modify that teaching by using the activin in conjunction with a further agent that promotes the reduction of scarring or further agent that promotes the healing of chronic wounds, as taught by

Ferguson, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because the overall process of wound healing is regulated by a number of growth factors and the combined administration of two or more scar reducing agents may be found to be even more effective or the combined administration of anti-scarring agent and a healing promoting agent would be expected to result in faster wound healing. The invention is prima facie obvious over the prior art.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
SEPTEMBER 21, 2006